FROM THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, SCHOOL OF MEDICINE

# Current Concepts in Viral Hepatitis

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■ *A great deal of interest and speculation has arisen from the discovery of a specific antigen, Australia antigen, in the serum of a high proportion of patients with viral hepatitis. This antigen has been found also in the serum of some patients with other conditions, including Down's syndrome, leukemia, leprosy, chronic renal disorders, and chronic active liver disease. It is not found in the serum of normal persons. Australia antigen has been postulated as the causative agent of viral hepatitis. In most patients the antigen can be detected for less than two weeks during the acute phase of the disease. Its persistence in other conditions may be due to an impairment of the immune response.*

*The course of acute viral hepatitis is usually uncomplicated, full recovery of liver function taking place within four to six weeks, with restoration of normal liver histology within three to four months. Follow-up studies of patients in whom hepatitis has developed during epidemics have failed to reveal evidence of subsequent chronic progressive liver disease. This suggests that most cases of chronic active hepatitis are not the result of preceding acute viral hepatitis. However, the recent finding of Australia antigen in the serum of a small number of patients raises the possibility that sporadic viral hepatitis may be one of the causes of the chronic active hepatitis. Alternatively, the presence of the antigen may be interpreted as being due to an altered immune response.*

*The treatment of acute hepatic coma remains unsatisfactory. Several new forms of therapy have been tried in recent years in an uncontrolled way. These include multiple exchange blood transfusions, isolated pig liver perfusion, human cross-circulation, and cross-circulation with baboons. Transient improvement may follow any of these procedures, but evidence that they influence the final outcome of the disease is lacking. The rapid fluctuations in the neurological status of individual patients makes it difficult to interpret the effects of therapy. Also, until satisfactory objective criteria of degrees of coma are universally accepted it will be impossible to compare one mode of therapy with another.*

DR. GERALD BEVAN (Division of Gastroenterology): We shall review current thoughts about some of the problems which continue to hinder our understanding and treatment of patients with viral hepatitis. Our remarks will be confined to the two common forms of this condition, infectious and serum hepatitis, although it should not be forgotten that hepatitis may be the dominant feature of other specific viral illnesses, including those due to Coxsackie B group viruses, herpes simplex virus, the viruses of infectious mononucleosis, cytomegalic inclusion disease, rubella, psittacosis, and probably also some adeno- and reo-viruses.

Unfortunately, the specific agent or agents producing hepatitis in the majority of patients still eludes identification, but the search for such an agent has been given new impetus by the discovery of a specific antigen, called Australia antigen, in the serum of many subjects exposed to the disease. The elucidation of the role of this antigen is going to prove a major landmark in the history of the disease. Dr. Gitnick will summarize what information is currently available about it. Before we move on to that, and in order to put it in perspective, we should remind ourselves how little we have understood the nature of hepatitis up to now.

Although the disease in an epidemic form has been recognized for centuries and has always been the scourge of armies in the field, it was not until World War II, just over 20 years ago, that it was finally considered to be primarily a disease of the liver. Until that time catarrhal jaundice, as it was called, was widely believed to result from obstruction of the ampulla and biliary passages by gastroduodenal inflammation, a view first propounded by Bamberger in 1855 and perpetuated by Virchow. Dissenting opinions were held by Botkin and Eppinger among others, but objective evidence of hepatitis was lacking until the introduction of closed liver biopsy by Iverson in 1939. Studies of large numbers of patients with hepatitis during World War II soon confirmed that the principal organ involved in catarrhal jaundice was the liver. During this period it was perceived also that the troublesome jaundice seen during the treatment of venereal disease, malaria and diabetes in large clinics, as well as the jaundice which sometimes followed the use of convalescent serum to treat or prevent infectious diseases, were similarly due to hepatitis. Virus as an etiologic factor was considered seriously for the first time as a result of transmission experiments using filtered serum and intestinal contents. Gamma globulin was used successfully to attenuate hepatitis of epidemic type, but was found to be variable in its effect on hepatitis associated with blood transfusion. Since World War II, epidemiological investigation has underlined differences between the two major forms of viral hepatitis, pointing to some important aspects of prevention, but by and large progress in understanding the disease process was arrested 20 years ago. The current work on Australia antigen, therefore, is a long-awaited breakthrough.

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## Australia Antigen

DR. GARY L. GITNICK (Division of Gastroenterology): The search for the agent, or agents, causing hepatitis has most recently focused on Australia antigen, Au(1). The characterization of this antigen is now being rapidly accomplished, but its story really began in 1961 in the laboratories of Drs. B. S. Blumberg and A. C. Allison[1] and was subsequently developed by Dr. Blumberg and his colleagues at the Institute for Cancer Research at Philadelphia.

In the early 1960s these scientists were exploring inherited variation in serum proteins. Allison and Blumberg postulated that individuals receiving multiple transfusions would receive serum proteins of a phenotype different from their own, and would respond by producing antibodies to these proteins. Using standard immunodiffusion techniques, they demonstrated a series of antigenic differences among the low-density beta lipoproteins. After demonstrating the presence of such lipoprotein antibodies, they also found precipitating antibodies against another unknown antigen in some of the human sera. These antibodies were present in highest frequency among hemophilia patients and in others who had received multiple transfusions.[2]

Blumberg and his colleagues found, in two multiply transfused hemophilia patients, precipitins reacting specifically with a single serum in their panel. In these instances, the antibody was directed, not against the serum lipoprotein, but against a new serum antigen. Since the antigen was first found in the serum of an Australian aborigine, it was designated "Australia antigen"—phenotype Au(1). The antibody to the antigen

was found to be associated with the IgG class of immunoglobulins.[3]

Population studies revealed that Au(1) was rarely present in normal populations in the United States, occurring in only two out of 2,000 normal people.[4] Au(1) has been detected in approximately 5 percent of apparently normal people in several Asian and oceanic countries, leading to studies suggesting Mendelian inheritance.[5] In contrast, the antigen was detected among 30 percent of 84 institutionalized patients with Down's syndrome, 18.4 percent of 38 patients with acute granulocytic leukemia, 13.3 percent of 30 patients with chronic lymphocytic leukemia, and 10.4 percent of 48 patients with acute hepatitis.[6] The frequency of Australia antigen has been found to be significantly higher in lepromatous leprosy than in tuberculoid leprosy.[7] Subsequent studies revealed that Australia antigen occurs transiently in post-transfusion hepatitis (58 percent) and infectious hepatitis (38 percent).[8] The association with hepatitis was quickly confirmed by Okochi and Murakami in Tokyo.[9] The Australia antigen complement fixation test has been introduced recently,[10] Shulman and his associates having demonstrated that by testing serial sera Au(1) could be detected in 98 percent of 130 patients with post-transfusion hepatitis. Sutnick and colleagues[11] found that Down's syndrome patients with Au(1) who had not received transfusions had chronic anicteric hepatitis.

Electron microscopic studies of partially purified antigen preparations revealed virus-like particles, 200 Angstrom units in diameter and agglutinable by specific antisera.[12] Immunofluorescence studies consistently demonstrated Au(1) in or on the nuclei of liver cells of patients with viral hepatitis and Australia antigen in their blood.[13] The antigen was not demonstrable in other forms of liver disease, either by immunofluorescent studies of liver preparations, or by evaluation of the blood of the patients using immunodiffusion. Prince,[14] using a similar method, demonstrated the presence of antigen in the serum only of patients with post-transfusion hepatitis, but not with infectious hepatitis; he designated this antigen as "SH" antigen. Subsequent studies have shown that SH antigen forms a band of identity with Australia antigen.[15,16] Because of the close association of Australia antigen with hepatitis, evidence that it can be transmitted by transfusion, its electron microscopic appearance, and its demonstration by immunofluorescence studies in the nuclei of liver cells, Sutnick, London, and Blumberg[17] suggested that the antigen may indeed be a virus which could be an etiologic agent of hepatitis.

Subsequent studies revealed the presence of the antigen in the blood of the personnel and patients in chronic hemodialysis units.[18] A number of laboratories have undertaken blood-donor screening programs, using the Au(1) test to screen potentially contaminated blood. Of recent interest has been the demonstration of the antigen among patients with chronic liver disease. Wright, McCollum, and Klatskin[16] and my colleagues and I[19] have demonstrated the presence of Australia antigen in the sera of 10 to 27 percent of patients with chronic active liver disease. In some of these patients, the antigen persists for months to years. Blumberg and his associates had already demonstrated the presence of the antigen among patients with Down's syndrome and anicteric chronic liver disease.[6] These findings have suggested that the agent may act as a slow or latent virus. Alternatively, London and his colleagues[18] have suggested that these findings, together with the frequent occurrence of Australia antigen among patients with Down's syndrome, leukemia, and lepromatous leprosy, indicate an association with some impairment of the immunologic system.

In support of that view, these investigators showed that the manifestations of hepatitis in patients as compared with the staff of hemodialysis units were impressively different. Whereas typical acute viral hepatitis developed in the staff, in patients the picture was that of chronic anicteric hepatitis. This was attributed to altered immune responsiveness. London and coworkers suggested that normal people, when infected with hepatitis virus, have an acute, self-limited disease with raised serum levels of transaminase and bilirubin, and Australia antigen persistence of less than two weeks. In contrast, patients with Down's syndrome, leukemia, lepromatous leprosy, and chronic renal disease, when infected, have a chronic disease characterized by lesser but prolonged elevations of serum transaminase and bilirubin, with persistence of Australia antigen for months to years. Blumberg and colleagues[5] had already presented evidence of inherited susceptibility to persistence of Au(1). London and his associates proposed, then, that the clinical features of viral hepatitis are largely determined by the host rather than the agent.

Over the past eight years, there has emerged a

picture of an unusual antigen found in a variety of populations but present in highest frequency in patients with hepatitis. Some of the patient populations among whom the antigen is found share a history of multiple blood transfusions. Blumberg now suggests that the common bond uniting all of the populations may be an immunological defect. What, then, is this immunological defect? Is it related to immediate, or (more likely) to delayed hypersensitivity? Or perhaps to a resistance factor not yet described? Is this antigen, which has so many characteristics suggestive of a virus, indeed an infectious agent? If so, why has it not been propagated in tissue culture and transmitted to animals? Is the antigen a subunit rather than a complete viral particle? Does it require the presence of another virus to manifest disease and to propagate in tissue culture and animals? Is the antigen merely a protein produced by the liver as a result of hepatocellular disease and, if so, why is it absent in other forms of liver disease? These questions are as yet unanswered, but will probably not remain so for long.

DR. BEVAN: I think these findings are very exciting. A great deal of work needs to be done in order to define the part played by Australia antigen in the pathogenesis of liver disease. Research in this field over the next few years is going to be most interesting. If it leads, as we all hope it will, to the development of a vaccine, this indeed would be a great triumph.

But, although we may feel that we are on the verge of a major advance in this disease, for the moment we have to accept continued bewilderment and therapeutic poverty when faced with it in a severe and unrelenting form.

Dr. Tillisch will now present the case history of a young girl who died recently in this hospital as a result of such a process.

## Case Presentation

DR. JAN H. TILLISCH (Department of Medicine): An 18-year-old Mexican woman was admitted to the UCLA hospital with a two-day history of lethargy and jaundice. Six weeks before admission she had begun to notice anorexia, fatigue, jaundice, dark urine and light stools. She was put into hospital in New Mexico for one week with a presumptive diagnosis of infectious hepatitis. Following discharge from hospital, jaundice cleared in approximately two weeks, the stools and urine returned to a normal color, and appetite improved. One week before admission to UCLA she felt entirely well. However, 36 hours before admission, her sister noted the recurrence of jaundice and the patient complained of feeling lethargic. Over the next few hours, lethargy increased and periods of disorientation occurred.

Past and family history were non-contributory. There had been no exposure to hepatotoxic agents.

On physical examination the patient was observed to be deeply jaundiced, semicomatose and occasionally delirious. Blood pressure was 120/60 mm of mercury, temperature was 38°C (100.4°F) and pulse rate 128. Petechiae and ecchymoses were present over the upper extremities and there was bleeding from the gums. Rhonchi were heard in both lower lung fields. Results of cardiac examination were normal. The abdomen was moderately distended and bowel sounds were hypoactive. Liver and spleen were not palpable. There was no peripheral edema. Neurological examination showed increased muscle tone and exaggerated deep tendon reflexes.

Significant laboratory data: Hematocrit 36 percent; hemoglobin 11.3 grams per 100 ml; leukocytes 17,900 per cu mm with segmented neutrophils 84 percent, lymphocytes 5 percent, monocytes 8 percent, banded forms 1 percent, basophils 1 percent. Platelets numbered 446,000 per cu mm. Prothrombin time was 49.3 seconds. Total serum bilirubin was 26 mg per 100 ml with direct 18 mg, and blood urea nitrogen (BUN) was 6.7 mg percent. Serum glutamic oxaloacetic transaminase (SGOT) was 570 units and serum glutamic pyruvic transaminase (SGPT) 2,740 units. Alkaline phosphatase was 28.4 units, albumin 3.3 grams per 100 ml, sodium 136.5 mEq, potassium 3.8 mEq, chloride 4.5 mEq and bicarbonate 7 mEq per liter.

Chest x-ray studies and an electrocardiogram were within normal limits. The patient was transfused with fresh, frozen plasma and fresh whole blood. Nasogastric aspiration produced guaiac-positive material. Vitamin K and dexamethasone were given intravenously. Shortly after admission the patient had a respiratory arrest thought to be due to retention of secretions. Intubation was carried out and positive pressure assistance was given constantly. Bicarbonate administration corrected the acidosis but her condition continued to deteriorate, coma deepening. Respiratory arrest occurred again and cardiac arrest followed. Attempts

at resuscitation were unsuccessful. The patient died approximately six hours after admission.

Postmortem examination showed massive hepatocellular necrosis, mild splenomegaly, pericardial and renal pelvic hemorrhages. There were no lesions in the central nervous system.

DR. BEVAN: Fortunately, the great majority of patients with viral hepatitis do not die from the disease. The mortality rate in epidemic and sporadic hepatitis is not more than one or two per thousand. For some unknown reason, death when it does occur is more common in females than in males. A higher mortality rate in serum hepatitis is understandably correlated with older age, the presence of underlying diseases, and drug administration. Most infections are either subclinical with no symptoms at all, or anicteric with minimal symptoms but no jaundice. Between massive hepatic necrosis leading to hepatic coma and death, on the one hand, and these mild infections on the other, lies a wide spectrum of pathological changes in the liver reflected in a variety of clinical syndromes. One of the outstanding controversial issues in this respect is whether or not acute hepatitis is ever followed by chronic liver disease. Clinical follow-up studies of soldiers who had hepatitis in the Middle East during World War II[20] and of survivors of the Delhi outbreak of 1955-6[21] suggest that chronic changes are rare, yet we all think we see such a progression from time to time in sporadic cases, especially in young women. It is possible that in these patients what appears to be sporadic acute hepatitis is in fact the first clinical manifestation of chronic hepatitis. Dr. Rosen will now discuss the spectrum of pathological changes that result from acute hepatitis. Perhaps he can illuminate for us the dark area between acute and chronic liver disease.

## Liver Disease Following Infectious Hepatitis

DR. VICTOR J. ROSEN (Department of Pathology at Mt. Sinai Hospital): In most patients with acute viral hepatitis recovery is assured: at least 95 percent recover completely without any clinical or pathological sequelae. In a small proportion of patients, mild clinical or biochemically detectable relapses may occur within one to four months after the acute illness, but in most instances these relapses cannot be considered manifestations of chronic hepatitis.

Only a small proportion of patients die of a massive hepatic necrosis following clinical viral hepatitis. Usually death occurs between one and two weeks after the attack. This hepatic alteration is commonly referred to as acute yellow atrophy because of the shrunken nature of the liver, with occasional yellow or tawny regenerative nodules apparent within the collapsed stroma. A more accurate term would be acute red necrosis, as the bulk of the liver shows massive necrosis rather than atrophy and the residual liver parenchyma has a highly vascular reddish background composed of collapsed reticulum, blood vessels and sinusoidal cells. The reason certain patients progress to this form of liver disease is not clear. In debilitated and elderly persons progression to acute yellow atrophy is more common than in previously healthy young adults.

Another rare but documented sequel of acute hepatitis is subacute hepatic necrosis occurring over a period of several weeks to months after an episode of acute viral hepatitis. In this situation, progression to a postnecrotic pattern of cirrhosis can be demonstrated by serial biopsy. In some patients, direct progression from acute hepatitis to subacute hepatic necrosis can be seen without a period of clinical latency. Pronounced collapse of liver parenchyma is noted in such patients, and fibrous connective tissue bridging between central lobular and periportal zones can be identified. These patients have a poor prognosis, many dying before extensive regenerative activity has occurred. Massive hepatic necrosis or subacute hepatic necrosis occur in approximately 1 percent of patients with clinical viral hepatitis.

A form of chronic liver disease develops in approximately 4 percent of patients who do not recover completely from acute hepatitis. In many of them the morphologic patterns are quite similar one to another, yet the clinical manifestations may be quite variable. Only subtle changes may distinguish the more serious and progressive chronic liver disease from the self-limited form. Many terms have been used for the chronic liver disease seen after viral hepatitis; these include chronic active or progressive hepatitis, chronic self-limited or non-progressive hepatitis, unresolved hepatitis, chronic autoimmune, lupoid, or plasma cell hepatitis, and asymptomatic chronic hepatitis or posthepatitic cirrhosis. It must be stated, however, that most of the patients who present with chronic forms of progressive and nonprogressive liver dis-

ease do not have a documented history of acute viral hepatitis.

The problem of chronic hepatitis was discussed in depth at the second meeting of the European Association for the Study of Liver Disease in 1968. Two basic forms of chronic hepatitis were distinguished. One was referred to as persistent chronic hepatitis with associated chronic portal inflammation, intact lobular architecture with no significant fibrosis, and occasionally features of acute hepatitis with minimal or absent piecemeal necrosis. The other category described was chronic aggressive hepatitis in which dense chronic inflammatory infiltrate was noted in portal tracts, extending into the parenchyma, with significant piecemeal necrosis occurring at the periphery of the lobules and with the formation of septal scars. Significant nodular regeneration was not observed in most of the patients in the latter category. It was felt that these two types of processes were of varied cause, possibly related to viral hepatitis in some cases. In many patients the morphologic pattern did not always correlate with the biochemical and clinical abnormalities. In addition, various nonspecific forms of reactive hepatitis, slowly resolving acute hepatitis, and drug hepatitis, could not always be distinguished from the two major groups described.

Many other clinical processes may also be related to sequelae of viral hepatitis. For example, it is conceivable that so-called primary biliary cirrhosis represents a variant of chronic active or persistent hepatitis with progressive bile ductular damage.

A possible relation between acute and chronic liver disease thus remains speculative for the present. In the future we must attempt to document more precisely the progressive pathologic and immunologic events which develop in some patients following acute liver disease.

DR. BEVAN: We turn now to the question of management of the complication of acute hepatitis shown by our patient—encephalopathy and coma.

The knowledge that the liver is capable of remarkable regeneration in a short space of time forms the basis of our approach to the management of patients developing signs of impending acute liver failure. Before discussing this in more detail, I would like to raise two problems that must be kept in mind. First of all, we can never be entirely certain, except possibly during an epidemic, that the patient in coma does have acute viral hepatitis. It sometimes turns out that we are witnessing an acute episode of a more chronic type of liver disease. For example, many patients with chronic active hepatitis come to the physician only when jaundice develops, and a long history of preceding illness is not always available. Second, when we go to the bedside of patients who have hepatitis with encephalopathy or coma, we take with us a philosophy of management based upon facts gathered very largely from the study of patients with chronic hepatic encephalopathy. It is worth remembering that it is by no means established that coma associated with acute liver disease and coma associated with chronic liver disease are due to a common metabolic derangement. Indeed, we are not entirely certain whether coma is the result of failure of the liver to extract a toxic product of some nature from the circulation, or of its failure to manufacture a vital component of cerebral metabolism, or even whether the liver itself is producing a toxin.

With these facts in mind it is clear that we should examine claims of new forms of therapy with some caution. Dr. Pops will evaluate some of the more heroic forms of therapy that have been tried in recent years to treat coma associated with potentially reversible disease of the liver.

## The Treatment of Hepatic Coma

DR. MARTIN A. POPS (Division of Gastroenterology): The association of central nervous system symptoms and severe liver disease has been recognized since ancient times. Fulminant hepatitis or acute yellow atrophy of the liver is the commonest cause of acute hepatic encephalopathy.

We now suspect that hepatic coma is associated with the inability of the liver to metabolize a variety of compounds such as ammonia, phenols and indoles which are absorbed from the gastrointestinal tract. Other factors that can worsen the encephalopathy produced by fulminant hepatitis are hypokalemia and alkalosis, hypotension, gastrointestinal bleeding, infection, and the administration of sedatives or narcotics.

The clinical manifestations are variable. They may include features of confusion, psychosis, altered consciousness which can progress to frank coma, a flapping tremor, hypertonicity and a characteristic fetor hepaticus or "hepatic breath." Similar neuropsychiatric signs may be seen in other conditions producing a metabolic encephal-

opathy, including uremia and pulmonary or circulatory failure.

*Accepted Methods of Therapy*

Methods of treatment of hepatic coma due to hepatitis are based upon the known biochemical abnormalities. They include elimination of protein from the diet and the oral or rectal administration of poorly absorbed antibiotics such as neomycin in the hope that these measures will reduce the bacterial degradation of protein within the large intestine. Glucose, often in hypertonic concentration, is given to provide an easily usable source of energy. Most physicians advise the use of purges and enemas to reduce further the bacterial population of the colon and to eliminate potentially cerebrotoxic nitrogenous material. Somewhat more controversial is the practice of giving large doses of corticosteroids; this has never been evaluated critically but there is no evidence of their being beneficial.

The results of such conservative treatment are said to be very poor in acute hepatic coma. Mortality as high as 90 percent has been reported in several series, so that it has become accepted that hepatic coma in viral hepatitis is an almost invariably fatal complication. This statement, which has virtually become a clinical dictum, should be, and has been, subjected to scrutiny for several reasons. First, there is no positive way to confirm the diagnosis of viral hepatitis; the work cited by Dr. Gitnick may eventually lead to a diagnostic test but, in the meantime, we must rely on historical and epidemiological evidence and a clinical picture which may be produced by a wide variety of hepatotoxic substances. Second, there is wide variability in the course and sequelae of the disease, making observations on relatively small groups of patients subject to inherent error. Third, there is no universally accepted system for grading hepatic coma; the encephalopathy can vary all the way from mild personality disturbances to decerebrate rigidity. Therefore, reports of the success or failure of a given therapeutic regimen, to be valid, should grade objectively the central nervous system abnormalities. Indeed, when attempts have been made to appraise the mortality in fulminant hepatitis in a more objective way, it would appear that earlier estimates were too pessimistic. Reynolds[22] questioned whether we really know what the mortality rate is; during an 18-month period, from 1966 to mid-1967, his group at the Los Angeles County General Hospital had a surprisingly low mortality rate—62 percent—among 16 patients with hepatic coma due to presumed viral hepatitis.[23] Reynolds pointed out that during the early stages of the comatose state there were no criteria, even in retrospect, that would allow one to predict which patients would survive. As the duration of coma increased, bleeding phenomena appeared, renal failure developed, and it became easier to predict a fatal outcome; but during the first day or two, when therapy might be most helpful, this was not possible.

*Newer Methods of Treatment*

Experience of this type is pertinent to a survey of the data now available on the more heroic forms of treatment of hepatic coma in viral hepatitis.

In 1966, reports of the treatment of hepatic coma by exchange blood transfusions were submitted by Trey[24] and Berger.[25] These investigators postulated that exchange transfusions in patients with acute yellow atrophy might remove sufficient "toxic" substances so that the patient can be kept alive long enough for regeneration of liver parenchyma to take place.

In March 1966, Berger and coworkers reported a seemingly miraculous recovery after two exchange transfusions over two days in a 25-year-old physician with fulminant hepatitis.[25] Multiple other modes of therapy had also been employed, including massive doses of corticosteroids. In the same issue of the *New England Journal of Medicine,* Trey, Burns, and Saunders[24] reported recovery in six of twelve patients similarly treated. To date, a total of approximately 20 recoveries from fulminant hepatic failure have been reported following exchange transfusion.

Reynolds pointed out that an unproved mode of therapy has become an accepted one even though no controlled experiments have been conducted.[22] One might answer that it would be inhuman for a physician to withhold potentially beneficial therapy for a fatal disease—a serious ethical problem for the doctor with such a patient. Also to be taken into consideration is the fact that arrangements must be made for the collection of 10 to 42 units of fresh, matched whole blood—a problem even for a large medical facility.

The mortality rate at Los Angeles County General Hospital is lower than the 77.5 percent figure recorded in the Second Progress Report of the Fulminant Hepatic Failure Surveillance Study organ-

ized by Dr. Trey in Boston.[26] This study is attempting to gather background data but it is in no sense a controlled trial of exchange transfusion therapy. Such a trial is now under way at the Los Angeles County-University of Southern California Medical Center, but it will be several years before it can provide any significant data.

Burnell and associates[27] reported in 1967 experiences with cross-circulation in three patients with fulminant hepatic coma. One patient survived after exchange of a total of 190 liters of blood, first with her husband and then with her father during 15 occasions over a ten-day period. This method of cross-circulation involves the insertion of an arteriovenous cannula into the forearm, as for renal hemodialysis. The patients are then connected artery-to-vein and vein-to-artery for cross-circulation. Changes in blood volume must be carefully monitored. The risk of immunologic reactions is great and did cause difficulties in the experience of Burnell and coworkers. Of course, the obvious disadvantage of cross-circulation is the risk to the normal partner. The clinical, social and moral issues involved in this procedure are complex and include known and unknown dangers.

Recently in the case of a young woman with probable halothane hepatitis we were about to attempt cross-circulation after the failure of three exchange transfusions, when our patient started to recover on her own and we cancelled the procedure. This points out the difficulties involved in assessing the efficacy of these forms of treatment. If we had actually begun the cross-circulation, say three to four hours earlier, we would still be congratulating ourselves on the miracle we had wrought.

Extracorporeal perfusion of an isolated pig liver preparation has been used by Eiseman[28] and others in an attempt to reverse hepatic coma resulting principally from cirrhosis, and also in some comatose patients with viral hepatitis. There have been no long-term survivors, although substantial but transient improvements in consciousness have occurred.

Finally, there have been at least three attempts at cross-circulation between humans and baboons.[29-31] This is the most complicated of the procedures described to date. It involves total exchange of the animal's blood volume with human blood matched with the patient's own blood, after washing out the baboon's circulation with Ringer lactate solution under hypothermia. The patient described by Bosman[29] awoke from very deep coma and appeared to make a satisfactory recovery initially, but died two months later. The other two cases were even less successful.

Transient improvement in neurological status often follows the use of one or another of the techniques described. It is less certain, however, whether any of these highly imaginative forms of treatment has any effect on the mortality of fulminant hepatitis.

For the moment, then, we are willing to consider these methods in the treatment of patients in coma who do not respond to conventional modes of therapy. But controlled studies using objective data are required before any of them can be strongly advocated.

## Discussion

DR. W. P. LONGMIRE, JR.: To what does Dr. Pops attribute the improving mortality figures for hepatic coma treated by conventional means?

DR. POPS: I believe this is due to several factors. First, there has been an improvement in the general care of seriously ill patients, frequently involving the use of intensive care units. Second, knowledge of the hematological problems raised by these patients and the means of treating them have increased. Also, it is now appreciated that early withdrawal of dietary protein and oral administration of broad spectrum antibiotics may reverse coma before the patient becomes obtunded.

DR. MIDDLER: Are there any early signs which help to distinguish those patients who are in most danger of developing coma and death?

DR. POPS: In my experience a falling urine output in the presence of adequate fluid replacement is an ominous sign. Of the laboratory tests, a rapidly rising serum bilirubin level often accompanies gross deterioration of liver function.

DR. BEVAN: One might add that a rising white cell count and a falling prothrombin index also presage a poor prognosis.

DR. A. F. RASMUSSEN, JR.: I wonder whether Dr. Gitnick would like to comment on the possibility that the effect of exchange transfusion may be due, in part, to the administration in the donor blood of lymphocytes previously sensitized to Australia antigen, since subclinical hepatitis infections are so common.

DR. GITNICK: That must remain an interesting speculation on the long-term effect of exchange transfusion.

DR. W. N. VALENTINE: This effect would presumably take some time to reveal itself, but the immediate effect of exchange transfusion when it occurs is more likely to be biochemical in nature.

DR. BEVAN: That is true. Perhaps the dramatic improvement in consciousness following exchange transfusion is due partly to the dilutional effect upon cerebral toxins, of which ammonia is thought to be the most important, and also to the correction of the acid-base disturbance frequently present in hepatic coma which may be aiding the transfer of such toxic substances across cell membranes.

DR. W. L. HEWITT: Dr. Gitnick, are there any other diseases in which virus particles have been demonstrated in the circulation? I wonder also whether there has been a prospective electron microscopy study of the time of appearance of circulating Australia antigen in hepatitis.

DR. GITNICK: Virus may be demonstrated in the serum of patients with several diseases by neutralization techniques, but I do not know of any instance of direct visualization of virus particles in blood. There has not yet been a prospective study of the time of appearance in the serum of Australia antigen as detected by electron microscopy. The data we have were derived by immunodiffusion and complement fixation techniques.

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